REMARKS

I. Status Summary

The present U.S. patent application is a divisional of U.S. Patent Application Serial Number 09/168,910, now U.S. Patent 6,270,758, filed October 8, 1998. Claims 64-84 are currently pending in the present application.

Claims 64, 72-76, and 80-84 have been allowed.

Claims 65-71 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while being enabled for methods using the cytokines IL-1α (applicants believe that there is a typographical error in the Official Action), IL-12, IL-15, IL-18, and combinations thereof, does not reasonably provide enablement for methods using "at least one other cytokine".

Claims 77-79 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite because the method steps are identical and it is not understood how administering the antigen/adjuvant composition intramucosally can result in each of a systemic, mucosal, and cell-mediated response separately.

No claims have been amended.

New claims 85-89 have been added. Support for the amendments can be found throughout the specification as filed, including particularly at page 15, lines 3-7. Additional support can be found in the claims as filed, including particularly claims 7 and 39. No new matter has been added as a result of the addition of the new claims.

Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Responses to the Rejection under 35 U.S.C. § 112, First Paragraph

Claims 65-71 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specification, while being enabled for methods using the cytokines IL-1α (applicants believe that there is a typographical error in the Official Action, which listed IL-1β instead of IL-1α), IL-12, IL-15, IL-18, and combinations

thereof, does not reasonably provide enablement for methods using "at least one other cytokine". Accordingly to the Patent Office, the enablement rejection is being made in view of applicants' remarks presented in response to the Patent Office's rejection in the previous Official Action that "it would be expected that if IL-1β is effective in the method of Gao, then any other interleukin would also be effective". The Patent Office thus asserts that it would not be predictable to the skilled artisan what other cytokines could be used in the claimed methods.

After careful review of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that in response to the rejection over the Gao reference in the previous Official Action, applicants stated the following:

> The Patent Office also asserts that since it would be expected that, if IL-1β is effective in the method of Gao, then any other interleukin would also be effective. Applicants respectfully submit that this assertion is not supported by any scientific evidence, nor by any teachings in the cited combination. Additionally, this assertion, even if it were true, assumes that the administration technique disclosed in Gao is the same as claimed in the instant application as asserted by the Patent Office. With reference to the discussion presented hereinabove, it is clear that the administration technique disclosed in Gao is not the same as claimed in the instant method, as Gao used subcutaneous administration and the instant claims recite intramucosal administration.

Response B at page 9 (emphasis added). Thus, applicants traversed the previous rejection under § 103 on at least two bases: first, that the Patent Office's assertion that "any other cytokine would also be effective" was not supported by reasonable scientific evidence or suggested by the cited documents; and second, that the "method of Gao" was not the method of claim 64 of the instant application. Thus, applicants respectfully submit that while it remains true that the Patent Office's previous assertion was unsupported, the lack of scientific support for the assertion was not the sole basis for applicants' traversal of the § 103 rejection. Instead, applicants' traversal was also based on the fact that the Patent Office was improperly attempting to extend the results disclosed in Gao to a method that recited a different mode of administration.

Stated another way, with regard to the Gao reference, applicants argued that subcutaneous administration of IL-1β did not render obvious mucosal administration of an adjuvant containing of IL-1α, IL-12, IL-15, IL-18, or combinations thereof. The basis for this statement is that there is no teaching in the cited references or in the art that any cytokine would be expected to have an equivalent activity when administered intramucosally as IL-1β had when administered subcutaneously as was disclosed in the Gao reference. Furthermore, applicants respectfully submit that the Patent Office's specific assertion that was traversed was the assertion that "if IL-1β is effective in the method of Gao, then any other interleukin would also be effective". Applicants respectfully submit that at best, the Patent Office might have asserted that if IL-1β is effective in the method of Gao then any other interleukin would also be effective in the method of Gao. Applicants respectfully submit, however, that the claimed method is not the method of Gao, and further that results obtained using the method of Gao are not necessarily predictive of the results expected from practicing the instant claims, particularly in view of the teachings of the Elson reference cited by the Patent Office that explicitly states that "most protein antigens are not only poor immunogens when given mucosally, but induce tolerance instead of immunity" (emphasis added).

Applicants respectfully submit that claims 65-71, the claims subject to the instant rejection, all depend directly or indirectly from claim 64. The rejected claims recite *inter alia* methods of eliciting an immune response against an antigen in a vertebrate subject by (a) providing an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, and IL-18 in combination with at least one other cytokine; and (b) administering said antigen-adjuvant composition intramucosally to the vertebrate subject in a manner such that initial contact occurs in mucosal tissue of the vertebrate subject. Thus, it would appear that the Patent Office is basing the instant rejection on applicants' prior traversal of the Patent Office's assertion that "any other cytokine would also be effective in the method of Gao". However, and as discussed in more detail herein, the methods recited in

claims 65-71 employ one of IL-1α, IL-12, IL-15, and IL-18 in combination with at least one other cytokine.

Applicants respectfully submit that their traversal of the Patent Office's assertion that "any other cytokine would also be effective in the method of Gao" is not inconsistent with their assertion that the instantly claimed methods, which recite the use of IL-1α, IL-12, IL-15, IL-18, or combinations thereof in combination with at least one other cytokine, are enabled. Applicants respectfully submit that the Patent Office concedes that the use of IL-1α, IL-12, IL-15, IL-18, or combinations thereof is enabled. Applicants further respectfully submit that given that these embodiments are enabled, the use of one or more additional cytokines in combination with the recited interleukin(s) is enabled because the instant specification itself provides the scientific support that the Patent Office's prior assertions lacked.

Stated another way, applicants respectfully submit that the Patent Office's broad assertion that any other cytokine employed alone would work as a mucosal adjuvant was not supported by reasonable scientific evidence or suggested by Gao, based in part on the different and in some cases opposing activities of different cytokines, and also in part on the fact that the method of Gao did not employ mucosal administration. The instant specification, on the other hand, does provide reasonable scientific support for the use of IL-1α, IL-12, IL-15, IL-18, or combinations thereof in combination with at least one other cytokine because the instant specification discloses that IL-1α, IL-12, IL-15, and IL-18, alone or in combination, function as mucosal adjuvants. Thus, applicants respectfully submit that since the recited interleukins, alone or in combination, function as an adjuvant when administered intramucosally, one of ordinary skill in the art would recognize what cytokines could be added.

Summarily, then, applicants respectfully submit that the § 103 rejection presented in the previous Official Action was addressed by pointing out that there is no reasonable scientific support for the assertion that the activity of IL-1β after subcutaneous administration implies that "any other interleukin" would have the same activity, particularly when administered intramucosally. Thus, applicants respectfully

submit that the Patent Office has based the current rejection of claims 65-71 under 35 U.S.C. § 112, first paragraph, on an improper premise. Applicants respectfully request that the rejection be withdrawn, and the claims allowed at this time.

However, even assuming *arguendo* that the Patent Office properly bases the instant rejection in part on applicants' prior statement, applicants respectfully submit the following remarks.

Initially, applicants respectfully draw the Patent Office's attention to the remarks presented hereinabove concerning the fact that the assertions made in the prior Official Action were based on the fact that no scientific support exists for the Patent Office's contention that any interleukin when administered intramucosally would be expected to have the same activity as subcutaneously administered IL-1β. Indeed, Elson provides direct evidence that those of skill in the art did not believe that intramucosally administered IL-1β would result in the elicitation of an immune response.

Furthermore, applicants respectfully submit that claims 65-71 do not claim replacing IL-1α, IL-12, IL-15, or IL-18 with other cytokines. Rather, the claims reciting adding "at least one other cytokine" to IL-1α, IL-12, IL-15, or IL-18. Applicants respectfully submit, and the Patent Office concedes, that the specification as filed clearly enables the use of IL-1α, IL-12, IL-15, IL-18, and combinations thereof. Applicants further respectfully submit that the specification as filed demonstrates that the use of IL-1α, IL-12, IL-15, or IL-18 alone, in combination with each other, or with other cytokines results in the elicitation of an immune response. Thus, it is not clear what aspect of adding an additional cytokine the Patent Office regards as not enabled. Applicants respectfully submit that the use of IL-1α, IL-12, IL-15, or IL-18 results in the activity of interest. Thus, the use of "at least one other" cytokine can augment this activity, as suggested in this specification where GM-CSF is administered and adjuvant activity is demonstrated.

Applicants respectfully submit that unlike the knowledge in the art prior to the instant disclosure, the current state of the art is now aware of the fact that IL-1α, IL-12, IL-15, or IL-18, and at least one other cytokine can be used in an antigen-adjuvant

composition to elicit immune responses by intramucosal administration. Thus, applicants respectfully submit that the instant specification removes the unpredictability surrounding the ability to elicit immune responses using intramucosal administration of antigen-adjuvant compositions comprising IL-1α, IL-12, IL-15, or IL-18 and at least one other cytokine that existed prior to the instant disclosure.

As a result, applicants respectfully submit that their statements regarding the state of the art prior to the instant disclosure do not support a rejection under 35 U.S.C. § 112, first paragraph, of the instant disclosure. Thus, applicants respectfully submit that claims 65-71 are enabled, and respectfully request that the instant rejection be withdrawn and the claims allowed at this time.

III. Response to the Rejection under 35 U.S.C. § 112, Second Paragraph

Claims 77-79 have been rejected under 35 U.S.C. § 112, second paragraph, upon the contention that the claims are indefinite. According to the Patent Office, the methods steps are identical, and it is not understood, given the recited steps, how administering an antigen/adjuvant composition intramucosally can result in each of a systemic, mucosal, and cell-mediated response separately. The Patent Office further asserts that all of these responses would occur simultaneously. Thus, the Patent Office contends that there is no difference in the method steps of claims 77-79.

After careful review of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Claim 64, the claim from which each of claims 77-79 depends, recites the following:

A method of eliciting an immune response against an antigen in a vertebrate subject, the method comprising:

(a) providing an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, IL-18 and combinations thereof; and

(b) administering said antigen-adjuvant composition intramucosally to the vertebrate subject in a manner such that initial contact occurs in mucosal tissue of the vertebrate subject, whereby an immune response is elicited.

Claims 77-79 recites that the immune response comprises a system immune response, a mucosal immune response, or a cell-mediated immune response, respectively. Thus, applicants respectfully submit that claim 77 essentially recites a method of eliciting an immune response against an antigen in a vertebrate subject, the method comprising: (a) providing an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, IL-18 and combinations thereof; and (b) administering said antigen-adjuvant composition intramucosally to the vertebrate subject in a manner such that initial contact occurs in mucosal tissue of the vertebrate subject, whereby a systemic immune response is elicited. Similarly, applicants respectfully submit that claim 78 essentially recites a method of eliciting an immune response against an antigen in a vertebrate subject, the method comprising: (a) providing an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, IL-18 and combinations thereof; and (b) administering said antigen-adjuvant composition intramucosally to the vertebrate subject in a manner such that initial contact occurs in mucosal tissue of the vertebrate subject, whereby a mucosal immune response is elicited. And finally, claim 79 recites a method of eliciting an immune response against an antigen in a vertebrate subject, the method comprising: (a) providing an antigen-adjuvant composition comprising the antigen and a cytokine adjuvant selected from the group consisting of IL-1α, IL-12, IL-15, IL-18 and combinations thereof; and (b) administering said antigen-adjuvant composition intramucosally to the vertebrate subject in a manner such that initial contact occurs in mucosal tissue of the vertebrate subject, whereby a cell-mediated immune response is elicited.

Applicants respectfully submit that each of the above claims particularly points out and distinctly claims the subject matter that applicants regard as the invention.

Applicants further respectfully submit that contrary to the Patent Office's apparent assertion, there is no requirement that the actual methods steps be different among the dependent claims, or that the nature of the immune response is such that the respective immune response types be capable of being elicited independently of each other. The Patent Office's attention is directed to the specific language of claims 77-79, in which the immune responses are recited as comprising a systemic, mucosal, or cell-mediated immune response.

Accordingly, applicants respectfully request that the rejection of claims 77-79 be withdrawn, and that the claims be allowed at this time. Applicants respectfully request a Notice of Allowance to that effect.

New Claims

New claims 85-88 have been added. Support for the amendments can be found throughout the specification as filed, including particularly at page 15, lines 3-7. Additional support can be found in the claims as filed, including particularly claims 7 and 39. No new matter has been added as a result of the addition of the new claims.

Applicants respectfully submit that the new claims are believed to be in condition for allowance for the reasons set forth hereinabove with regard to claims 64-84. Accordingly, applicants respectfully submit that claims 64-88 are in condition for allowance, and respectfully request a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Serial No.: 09/874,103

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
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